III. REMARKS/ARGUMENTS

Claims 1 and 42-62 are pending. The claims have been amended in order to correct dependencies due to the renumbering of the previously submitted claims.

Rejection Under 35 U.S.C. § 103(a)

In the Office Action, the Examiner rejected claims 1 and 42-62 under 35 U.S.C. § 103(a) as being unpatentable over Raffa *et al.* ((Caplus 1992:120745, J. Pharmacol. Exp. Ther. 1992, 260 (1), 275-85)) in view of EP 0147780 to Bondi ("the Bondi reference"). The Examiner's rejection was based on his previous Office Actions mailed April 23, 2002 and January 14, 2003. In the previous Office Actions the Examiner stated that "Raffa et al teach the use of Tramadol hydrochloride as a pain medicament with opioid and nonopioid properties... The instant claimed invention differs from the prior art by requiring a controlled release composition... The secondary reference to Bondi teaches a controlled release method for a variety of compounds of which Tramadol is listed as an example... It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used the controlled release method taught in Bondi for making an oral composition of Tramadol... The claims drawn to specific amounts, specific dosage forms, specific dissolution rates etc., are all obvious since a skilled artisan would reasonably be expected to tweak the controlled release form of Tramadol [of Bondi] to meet a variety of needs"

The Examiner's rejection is respectfully traversed.

Independent claim 1 recites: "*a solid controlled release oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a matrix, said dosage form providing a therapeutic effect for at least about 24 hours.*" (Emphasis Added)

Independent claim 52 recites: "*a solid controlled release oral dosage form, comprising a therapeutically effective amount of tramadol or a pharmaceutically acceptable salt thereof incorporated into a matrix, said dosage form providing a therapeutic effect for at least about 12 hours.*" (Emphasis Added)

The Bondi reference describes controlled release compositions for release of drugs through a rate limiting barrier by coating a formulation with a coating comprising polyvinyl alcohol, which serves as a membrane or barrier film which selectively permits passage of the drug. Although the specification of this reference states that the drug may be dispersed homogeneously throughout a matrix composed of polyvinyl alcohol, this embodiment is not exemplified. All of the examples are directed to formulations comprising film coatings which comprise polyvinyl alcohol.

Tramadol limitation

The Bondi reference describes that the reference is suitable for use with, but not limited to, a large genus of possible active agents. This genus is listed in the Bondi reference starting on page 5, line 24 to page 9, line 16. This exhaustive genus includes many hundreds of compounds Accordingly, the recitation of tramadol (page 7, line 30) is merely a single species of the large genus described in the Bondi reference.

It is respectfully submitted that one skilled in the art would not be motivated to select the particular claimed species (i.e. tramadol) from the large genus disclosed on pages 5-9 of the Bondi reference and combine this reference with the Raffa reference. In support of this position, it is respectfully submitted that with respect to Bondi, (i) the size of the genus is not sufficiently small as to render each member of the genus inherently disclosed, (ii) the reference does not expressly teach a particular reason to select the claimed species; and (iii) there is no teaching of structural similarity in the reference. A discussion of these points follows:

(i) The size of the genus is not sufficiently small as to render each member of the genus inherently disclosed

The fact that a claimed species is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). Some motivation to select the

claimed species or subgenus must be taught by the prior art. See e.g., *In re Deuel*, 51 F.3d at 1558-59, 34 USPQ2d at 1215.

It has been held that a prior art genus containing only 20 compounds inherently anticipated a claimed species within the genus. *In re Petering*, 301 F.2d 676,681, 133 USPQ 275, 280 (CCPA 1962). As presented above, the Bondi reference describes a genus including many hundreds of compounds. It is respectfully submitted that the Bondi reference does not render obvious each and every individual species (e.g. tramadol) which falls within their broad genus, based on the size of the genus. Therefore, one skilled in the art would not select tramadol from the Bondi reference and combine the Raffa reference.

(ii) The reference does not expressly teach a particular reason to select the claimed species

If a prior art reference expressly teaches a particular reason to select the claimed species, the Examiner should point out the express disclosure which would have motivated one of ordinary skill in the art to select the claimed species. See MPEP 8th Edition, 1st revision 2144.08 II (A)(4)(B). It is respectfully submitted that the only recitation of tramadol in the Bondi reference is embedded within a large genus. Accordingly, the Bondi reference does not expressly teach a particular reason to select tramadol from the plethora of other possible species in the genus of the reference and combine this reference with the Raffa reference.

(iii) There is no teaching of structural similarity in the reference

If a preferred species is structurally similar to that claimed, its disclosure may motivate one of ordinary skill in the art to choose the claimed species from the genus. See, e.g., *In re Dillon*, 919 F.2d at 693, 696, 16 USPQ2d at 1901, 1904. It is noted that the preferred active agents exemplified in the Bondi reference are L-dopa and timolol maleate in Examples 1 and 2 respectively.

It is respectively submitted that L-dopa (3-hydroxy-L-tyrosine, an anti-parkinsonian) and timolol maleate ((S)-1-[(1,1-dimethylethyl)amino]-3-[[4-(4-morpholinyl)- 1,2,5-thiadiazol -3 -yl]oxy]-2-propanol maleate, a beta-blocker) are not similar in structure to tramadol (i.e., (+)-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol). Accordingly, as the Bondi reference does not teach any preferred species which have structural similarity to tramadol, there is no motivation therein to one skilled in the art to select tramadol from the large genus therein and combine this reference with the Raffa reference.

Further, any teaching or suggestion in the reference of a preferred species that is significantly different in structure from the claimed species weigh against selecting the later selected species. Baird, 16 F.3d 382-83, 29 USPQ2d 1552 (Fed. Cir. 1994). Accordingly, the examples of the Bondi reference directed to compounds that are not structurally similar to tramadol is further evidence that one skilled in the art would not be motivated to select tramadol from the genus described therein.

12 hour and 24 hour limitations

The Bondi reference does not teach, hint or suggest that the delivery systems described therein provide a therapeutic effect of the active agent for a period of at least about 12 or about 24 hours as claimed in independent claims 52 and 1, respectively. There are no clinical trials reported therein, there are no indications that the dosage forms described therein were ever administered to human subjects, and there is no teaching or suggestion of any desired pharmacokinetic parameters reported in Bondi. Therefore, a combination of the Raffa reference with the Bondi reference would not result in a dosage form which provides a therapeutic effect of the active agent for a period of at least about 12 or about 24 hours.

In addition, the Examiner has not provided any motivation to obtain a dosage form comprising tramadol which provides a therapeutic effect for a period of at least about 12 or about 24 hours. It is noted that the factual question of motivation is material to patentability, and cannot be resolved on subjective belief and unknown authority and that the Examiner must explain reasons why one of ordinary skill in the art would have

been motivated to select references and to combine them to render the claimed invention obvious. See *In Re Lee*, 61 USPQ2d 1430, (Fed. Cir. 2002).

It is respectfully submitted that the Examiner has not provided any objective authority (e.g., a secondary reference) in combination with the Raffa and Bondi references which would provide motivation to one skilled in the art to arrive at the claimed pharmacokinetic parameters (i.e., a therapeutic effect of tramadol for at least 12 or 24 hour).

In fact, it is respectfully submitted that the formulations described in the Bondi reference do not exhibit or enable 12 to 24 hour controlled release dosage forms. This is supported by the enclosed Declaration (Exhibit A) of Dr. Sandra Malkowska, which was previously submitted during the prosecution of the parent case, U.S. Patent Application Serial No. 08/241,129, filed May 10, 1994, now U.S. Patent No. 5,591,452 and the corresponding European case, European Patent Application No. 94303128.6, now EP 0 624 366. Ms. Malkowska is one of the named inventors in the presently claimed invention.

Exhibit A demonstrates that practical attempts on behalf of inventor Malkowska to produce sustained release compositions in accordance with the teachings of the Bondi reference resulted in a product which released greater than 90% active agent after 2 hours. Tablets were prepared using the formula and process of Example 1 of the Bondi reference, but replacing the L-dopa with tramadol hydrochloride. The dissolution rates obtained from Experiments 1 and 2 were as follows:

Table I

	Product- Experiment 2	Product- Experiment 1
Hour		
1	88	59
2	98	91
3	99	102
4	99	107
5	99	109
6	99	110

As demonstrated above, the tramadol formulations of the Malkowska declaration resulted in products which resulted in 88 % tramadol released at 1 hour and 91 % tramadol released at 2 hours. Although in-vitro results cannot predict in-vivo results, in-vitro parameters are used as an indication of what formulations would be suitable for further testing. It is respectfully submitted that one skilled in the art would not subject the above formulations to further testing as there is no indication that such formulations would be suitable for 12 or 24 hour formulations, based on the in-vitro result of 88 % tramadol released at 1 hour and 91 % tramadol released at 2 hours for the experimental formulations.

Accordingly, it is respectfully submitted that the Bondi reference does not exhibit or enable formulations which provide a therapeutic effect for at least 12 or 24 hours as presently claimed. Therefore, a combination of the Raffa reference with the Bondi reference would not result in a dosage form which provides a therapeutic effect of the active agent for a period of at least about 12 or about 24 hours.

IV. CONCLUSION

It is now believed that the above-referenced rejections have been obviated and it is respectfully requested that the rejections be withdrawn. It is believed that all claims are now in condition for allowance.

Enclosed is a check in the amount of $1280.00 to cover the fee for the three-month extension of time and Notice of Appeal.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Robert J. Paradiso
Reg. No. 41,240

Davidson, Davidson & Kappel, LLC
485 Seventh Avenue, 14th Floor
New York, New York 10018
(212) 736-1940